MALARIA

DISEASE REPORTING

In Washington

DOH receives approximately 30 to 50 reports of malaria per year. The last Washington death associated with malaria occurred in 1980.

Cases are associated with travel to endemic areas as malaria almost never occurs in the United States. Recent cases have been exposed to mosquitoes, blood transfusions, or shared needles in Africa, Asia, Central and South America, and Mexico.

Purpose of reporting and surveillance

- To assist in the diagnosis and treatment of cases, particularly those with potentially serious malarial infections.
- To identify others who may benefit from screening or treatment, e.g., fellow travelers or recipients of blood products.
- To educate people about how to reduce their risk of infection.

Reporting requirements

- Health care providers: notifiable to Local Health Jurisdiction within 3 work days
- Hospitals: notifiable to Local Health Jurisdiction within 3 work days
- Laboratories: no requirements for reporting
- Local health jurisdictions: notifiable to DOH Communicable Disease Epidemiology within 7 days of case investigation completion or summary information required within 21 days

CASE DEFINITION FOR SURVEILLANCE

Clinical criteria for diagnosis

Signs and symptoms are variable; however, most patients experience fever. In addition to fever, common associated symptoms include headache, back pain, chills, sweats, myalgia, nausea, vomiting, diarrhea, and cough. Untreated *Plasmodium falciparum* infection can lead to coma, renal failure, pulmonary edema, and death. The diagnosis of malaria should be considered for any person who has these symptoms and who has traveled to an area in which malaria is endemic. Asymptomatic parasitemia can occur among persons who have been long-term residents of areas in which malaria is endemic.

Laboratory criteria for diagnosis

- Demonstration of malaria parasites in blood films.

Case definition

- Confirmed: an episode of microscopically confirmed malaria parasitemia in any person (symptomatic or asymptomatic) diagnosed in the United States, regardless of whether the person experienced previous episodes of malaria while outside the country.

  A subsequent attack experienced by the same person but caused by a different Plasmodium *species is counted as an additional case. A subsequent attack experienced by the same person and caused by the same species in the United States may indicate a relapsing infection or treatment failure caused by drug resistance. Blood smears from questionable cases should be referred to the National Malaria Repository, CDC, for confirmation of the diagnosis. Cases also are classified according to the following World Health Organization categories:*
  - ***Autochthonous****:*
    - ***Indigenous****: malaria acquired by mosquito transmission in an area where malaria is a regular occurrence*
    - ***Introduced****: malaria acquired by mosquito transmission from an imported case in an area where malaria is not a regular occurrence*
  - ***Imported****: malaria acquired outside a specific area (e.g., the United States and its territories)*
  - ***Induced****: malaria acquired through artificial means (e.g., blood transfusion, common syringes, or malariotherapy)*
  - ***Relapsing****: renewed manifestation (i.e., of clinical symptoms and/or parasitemia) of malarial infection that is separated from previous manifestations of the same infection by an interval greater than any interval resulting from the normal periodicity of the paroxysms*
  - ***Cryptic****: an isolated case of malaria that cannot be epidemiologically linked to additional cases.*

A. DESCRIPTION

1. Identification

A parasitic disease; infections with the four human malarias can present sufficiently similar symptoms to make species differentiation generally impossible without laboratory studies. Furthermore, the fever pattern of the first few days of infection resembles that seen in early stages of many other illnesses (bacterial, viral and parasitic). Even the demonstration of parasites, particularly in highly malarious areas, does not necessarily mean that malaria is the patient's sole illness (e.g., early yellow fever, Lassa fever, typhoid fever). The most serious malarial infection, falciparum malaria (malignant tertian) may present a quite varied clinical picture, including fever, chills, sweats, cough, diarrhea, respiratory distress and headache, and may progress to icterus, coagulation defects, shock, renal and liver failure, acute encephalopathy, pulmonary and cerebral edema, coma and death. It is a possible cause of coma and other CNS symptoms, such as disorientation and delirium, in any nonimmune person recently returned from a tropical area. Prompt treatment is essential, even in mild cases, since irreversible complications may appear suddenly; case-fatality rates among untreated children and nonimmune adults can be 10%-40% or higher.

The other human malarias, vivax (benign tertian), malariae (quartan) and ovale, generally are not life-threatening. Illness may begin with indefinite malaise and a slowly

rising fever of several days' duration, followed by a shaking chill and rapidly rising temperature, usually accompanied by headache and nausea, and ending with profuse sweating. After an interval free of fever, the cycle of chills, fever and sweating is repeated, either daily, every other day or every third day. Duration of an untreated primary attack varies from a week to a month or longer. True relapses following periods with no parasitemia (seen with vivax and ovale infections) may occur at irregular intervals for up to 5 years. Malariae infections may persist for life with or without recurrent febrile episodes.

Persons who are partially immune or who have been taking prophylactic drugs may show an atypical clinical picture and a prolonged incubation period.

Laboratory confirmation of the diagnosis is made by demonstration of malaria parasites in blood films. Repeated microscopic examinations every 12-24 hours may be necessary because the density of *Plasmodium falciparum* parasites in the peripheral blood varies and parasites are often not demonstrable in films from patients recently or actively under treatment. Several tests are under study. The most promising are dipsticks that detect circulating plasmodial antigens in the bloodstream. While licensed abroad, none were, as of late 1999, licensed in the US. Diagnosis by PCR is the most sensitive method available, but is a specialized assay not generally available in diagnostic laboratories. Antibodies, demonstrable by IFA or other tests, may appear after the first week of infection but may persist for years, indicating past malarial experience; thus antibody determinations are not helpful for diagnosis of current illness.

2. Infectious Agent

Plasmodium vivax, *P. malariae*, *P. falciparum* and *P. ovale*; sporozoan parasites. Mixed infections are not infrequent in endemic areas.

3. Worldwide Occurrence

Endemic malaria no longer occurs in many temperate-zone countries and in some areas of subtropical countries, but is still a major cause of ill health in many tropical and subtropical areas; high transmission areas are found on the fringes of forests in South America (e.g., Brazil), southeast Asia (e.g., Thailand and Indonesia) and throughout sub-Saharan Africa. Ovale malaria occurs mainly in sub-Saharan Africa where vivax malaria is much less frequent.

P. falciparum refractory to cure with the 4 aminoquinolines (such as chloroquine) and other antimalarial drugs (such as sulfa-pyrimethamine combinations and mefloquine) occurs in the tropical portions of both hemispheres, particularly in the Amazon region and parts of Thailand and Cambodia. *P. vivax* refractory to treatment with chloroquine is present in Papua New Guinea and is prevalent in Irian Jaya (Indonesia) and has been reported from Sumatra (Indonesia), the Solomon Islands, and Guyana. The hepatic stages of some *P. vivax* strains may also be relatively resistant to treatment with primaquine. In the US, a few episodes of locally acquired malaria have occurred since the mid-1980s. Current information on foci of drug-resistant malaria is published annually by WHO and can also be

obtained from the Malaria Section, CDC, Atlanta or by consulting the CDC's travel web site: http://www.cdc.gov/travel.

4. Reservoir

Humans are the only important reservoir of human malaria. Nonhuman primates are naturally infected by many malarial species, including *P. knowlesi*, *P. cynomolgi*, *P. brazilianum*, *P. inui*, *P. schwetzi* and *P. simium*, which can infect humans experimentally, but natural transmission to humans is rare.

5. Mode of Transmission

By the bite of an infective female *Anopheles* mosquito. Most species feed at dusk and during early night hours; some important vectors have biting peaks around midnight or the early hours of the morning. When a female *Anopheles* mosquito ingests blood containing the sexual stages of the parasite (gametocytes), male and female gametes unite to form the ookinete in the mosquito stomach which then penetrates the stomach wall to form a cyst on the outer surface in which thousands of sporozoites develop; this requires 8-35 days, depending on the species of parasite and the temperature to which the vector is exposed. These sporozoites migrate to various organs of the infected mosquito, and some that reach the salivary glands mature and are infective when injected into a person as the insect takes the next blood meal.

In the susceptible host, the sporozoites enter liver hepatocytes and develop into exoerythrocytic schizonts. The hepatocytes rupture and asexual parasites (tissue merozoites) reach the bloodstream through the hepatic sinusoids and invade the erythrocytes to grow and multiply cyclically. Most will develop into asexual forms, from trophozoites to mature blood schizonts that rupture the erythrocyte within 48-72 hours, to release 8-30 (depending on the species) free erythrocytic merozoites that invade other erythrocytes. Clinical symptoms are produced at the time of each cycle, by the rupture of large numbers of erythrocytic schizonts. Within infected erythrocytes, some of the merozoites may develop into the male (microgametocyte) or the female (macrogametocyte), the sexual forms.

The period between the infective bite and the detection of the parasite in a thick blood smear is the prepatent period, which is generally 6-12 days with *P. falciparum*, 8-12 days with *P. vivax* and *P. ovale*, and 12-16 days with *P. malariae* (but may be shorter or longer). Delayed primary attacks of some *P. vivax* strains may occur 6-12 months after exposure. Gametocytes usually appear in the blood stream within 3 days of parasitemia with *P. vivax* and *P. ovale*, and after 10-14 days with *P. falciparum*. Some exoerythrocytic forms of *P. vivax* and *P. ovale* exist as dormant forms (hypnozoites) that remain in hepatocytes to mature months or years later and produce relapses. This phenomenon does not occur in falciparum or malariae malaria, and reappearance of these forms of the disease is the result of inadequate treatment or of infection with drug-resistant strains. With *P. malariae*, low levels of erythrocytic parasites may persist for many years, to multiply at some future time to a level that may result again in clinical illness. Malaria may also be transmitted by

injection or transfusion of blood from infected persons or by use of contaminated needles and syringes, as by injecting drug users. Congenital transmission occurs rarely, but stillbirth from infected mothers is more frequent.

6. Incubation period

The time between the infective bite and the appearance of clinical symptoms is approximately 7-14 days for *P. falciparum*, 8-14 days for *P. vivax* and *P. ovale*, and 7-30 days for *P. malariae*. With some strains of *P. vivax*, mostly from temperate areas, there may be a protracted incubation period of 8-10 months. With infection by blood transfusion, incubation periods depend on the number of parasites infused and are usually short, but may range up to about 2 months. Suboptimal drug suppression, such as from prophylaxis, may result in a prolonged incubation period.

7. Period of communicability

For infectivity of mosquitoes, as long as infective gametocytes are present in the blood of patients; this varies with species and strain of parasite and with response to therapy. Untreated or insufficiently treated patients may be a source of mosquito infection for more than 3 years in malariae, 1-2 years in vivax, and generally not more than 1 year in falciparum malaria; the mosquito remains infective for life. Transmission by transfusion may occur as long as asexual forms remain in the circulating blood; with *P. malariae* this can continue for 40 years or longer. Stored blood can remain infective for at least a month.

8. Susceptibility and resistance

Susceptibility is universal except in humans with specific genetic traits. Tolerance or refractoriness to clinical disease is present in adults in highly endemic communities where exposure to infective anophelines is continuous over many years. Most black Africans show a natural resistance to infection with *P. vivax*, which is associated with the absence of Duffy factor on their erythrocytes. Persons with sickle cell trait have relatively low parasitemia when infected with *P. falciparum*, and therefore are relatively protected from severe disease.

B. METHODS OF CONTROL

1. Preventive measures:

I. Community based measures

a. Encourage source reduction and control of larval stages by sanitary improvements that will result in permanent elimination or reduction of anopheline mosquito breeding habitats close to human population settlements. Methods to eliminate unusable impounded water (filling in and draining) and to increase the speed that water flows in natural or artificial channels (rectification and clearing of path and margins) are very effective adjunct measures for permanent malaria control. Use of

chemical and biological control methods on useful impounded water requires more recurrent cost and efforts than the maintenance required for permanent elimination of breeding sites, but is another important adjunct to malaria control at the local level of transmission.

b. Any large scale use of residual insecticides against adult anopheline vectors should be preceded by a careful appraisal of the transmission characteristics in the problem area. Even in those transmission foci characterized by mosquitoes that tend to rest and feed indoors (endophilic and endophagic vectors), the sole application of residual insecticides on the inside walls of dwellings may not necessarily result in permanent malaria control. Residual insecticide on the inside walls of dwellings and on other surfaces will generally be ineffective where the vector has developed resistance to these insecticides or the vectors do not enter houses.
c. Other important considerations of an integrated control plan should include:
    i. Access to health care services for early diagnosis and prompt treatment.
    ii. Intersectoral epidemiologic monitoring of human population movement patterns (migration and circulation): these are the source of introduction and spread of *Plasmodium* spp. into areas ecologically prone to transmission.
    iii. Massive public information measures directed to those exposed to risk on how best to protect themselves, their families and their community.
    iv. Prompt and effective treatment of acute and chronic cases is an important measure of malaria control. Moreover, the mortality from all *P. falciparum* infections is strongly associated with delayed diagnosis and delay in receiving effective treatment.
    v. Blood donors should be questioned for a history of malaria or a history of travel to, or residence in a malarious area. In most nonendemic areas, travelers who have not taken antimalarial drugs and have been free of symptoms may donate 6 months (in the US, this period is 1 year) after return from an endemic area. For long term (more than 6 months) visitors to malarious areas who have been on antimalarials and have not had malaria, or for persons who have immigrated or are visiting from an endemic area, they may be accepted as donors 3 years after cessation of prophylactic antimalarial drugs and departure from the endemic area, if they have remained asymptomatic. A period of more than 6 months is considered residence in a malarious area, and the donor should be evaluated as an immigrant from that area. An immigrant or visitor from an area where malariae malaria is or had been endemic may be a source of transfusion induced infection for many years. Such areas include but are not limited to malaria endemic countries of the Americas, tropical Africa, Papua New Guinea, south and southeast Asia and even countries of the Mediterranean region of Europe, where malariae transmission no longer occurs.

II. Personal protective measures

Because of the resurgence of malaria during the past decade, the following guidelines on prevention, especially prophylaxis and treatment are presented in detail. Travelers to malarious areas need to realize that: protection from biting mosquitoes continues to be of paramount importance; no antimalarial prophylactic regimen gives

complete protection; prophylaxis with antimalarial drugs should not automatically be prescribed for all travelers to malarious areas; and standby or emergency self-treatment is recommended when a febrile illness occurs in a falciparum malaria area where professional medical care is not readily available.

a. Measures to reduce the risk of mosquito bites include:
    i. Avoid going out between dusk and dawn when anopheline mosquitoes commonly bite. Wear long sleeved clothing and long trousers when going out at night, and avoid dark colors which attract mosquitoes.
    ii. Apply insect repellent to exposed skin; choose one containing either N, N-diethyl-m-toluamide (Deet) or dimethyl phthalate. The manufacturers' recommendations for use must not be exceeded, particularly with small children.
    iii. Stay in a well-constructed and well-maintained building in the most developed part of town.
    iv. Use screens over doors and windows; if no screens are available, close windows and doors at night.
    v. If accommodation allows entry of mosquitoes, use a mosquito net over the bed, with edges tucked in under the mattress, and ensure that the net is not torn and that there are no mosquitoes inside it; increased protection may be obtained by impregnating the net with synthetic pyrethroid insecticides.
    vi. Use antimosquito sprays or insecticide dispensers (mains or battery operated) that contain tablets impregnated with pyrethroids, or burn pyrethroids, or pyrethroid mosquito coils in bedrooms at night.
b. People who are or will be exposed to mosquitoes in malarious areas should be given the following information:
    i. The risk of malaria infection varies among countries and within different areas of each country. See country list in WHO's annual publication International Travel and Health, ISBN-9241580208.
    ii. Pregnant women and young children when exposed and infected are highly susceptible to development of severe and complicated malaria (see below).
    iii. Malaria can kill if treatment is delayed. Medical help must be sought promptly if malaria is suspected; a blood sample should be examined for malaria parasites on more than one occasion and a few hours apart.
    iv. Symptoms of malaria may be mild; malaria should be suspected if, 1 week after entry into a transmission area, an individual suffers any fever, malaise with or without headache, backache, muscular aching and/or weakness, vomiting, diarrhea and cough. Prompt medical advice must be sought.
c. Pregnant women and parents of young children should be advised of the following:
    i. Malaria in a pregnant woman increases the risk of maternal death, miscarriage, stillbirth and neonatal death.
    ii. A malarious area should not be visited unless absolutely necessary.
    iii. Extra diligence is needed in using measures to protect against mosquito bites.
    iv. Chloroquine (5.0 mg/kg/week-the equivalent of 8.0 mg of diphosphate salt/kg/week; 6.8 mg of sulphate salt/kg/week and 6.1 of hydrochloride salt/kg/week) and proguanil (3.0 mg/kg/day-the equivalent of 3.4 mg of

hydrochloride salt/kg/day) should be taken for prophylaxis (proguanil alone is not available in the US, however, atovaquone/proguanil has been approved for infants weighing ≥11 kg). In areas with chloroquine-resistant *P. falciparum*, chloroquine and proguanil should be taken during the first 3 months of pregnancy; mefloquine prophylaxis (5.0 mg/kg/week-the equivalent of 5.48 mg of hydrochloride salt/kg/week) may be considered; start from the fourth month of pregnancy.

v. Doxycycline prophylaxis should not be taken.

vi. Medical help should be sought immediately if malaria is suspected; emergency ”standby” treatment should be taken only if no medical help is immediately available. Medical help must still be sought as soon as possible after standby treatment (see B1(II)d and B1(II)e below).

vii. Malaria prophylaxis is important for the protection of young children. Chloroquine (5 mg/kg/week) plus proguanil (3 mg/kg/day) may be given safely to infants (proguanil is not available in the US).

viii. Mefloquine prophylaxis (5 mg/kg/week) may be taken by women of childbearing age, but pregnancy should be avoided for 3 months after stopping the drug. Cumulative evidence from women inadvertently given mefloquine chemoprophylaxis during pregnancy and from clinical trials has not shown embryotoxic or teratogenic effects. Mefloquine may therefore be given during the second and third trimesters. Data concerning use during the first trimester are limited, but in situations of inadvertent pregnancy, prophylaxis with mefloquine is not considered an indication for pregnancy termination.

ix. Doxycycline prophylaxis (1.5 mg dihydrochloride salt/kg/day) may be taken by women of childbearing age, but pregnancy should be avoided for about 1 week after stopping the drug.

x. If pregnancy occurs during antimalarial prophylaxis (except with chloroquine plus proguanil), information about congenital risks should be sought from the drug manufacturer by the woman's doctor.

d. Standby treatment: The most important factors that determine the survival of patients with falciparum malaria are early diagnosis and immediate treatment. Most nonimmune individuals exposed to or infected with malaria should be able to obtain prompt medical attention when malaria is suspected. However, a minority will be exposed to a high risk of infection, and will be at least 12-24 hours away from competent medical attention. In such cases, WHO recommends that prescribers issue antimalarial drugs to be carried by the persons who may be in such exposed situations for self-administration. Persons prescribed such standby treatment should be given precise instructions on the recognition of symptoms, the complete treatment regimen to be taken, possible side effects and the action to be taken in the event of drug failure. Moreover, they should be made aware that self-treatment is a temporary measure and medical advice is still to be sought as soon as possible.

e. Prophylaxis: Nonimmune individuals who will be exposed to mosquitoes in malarious areas must make use of the protective measures against mosquito bites and could also benefit from the use of suppressive drugs for chemoprophylaxis. The possible side effects of long term (up to 3 to 5 months) use of the drug or drug combination

recommended for use in any particular area should be weighed against the actual likelihood of being bitten by an infected mosquito. There may be no risk of exposure to those visitors or residents in most urban areas in many malarious countries, including southeast Asia and South America, so suppressive drugs may not be indicated. In some urban centers, notably in Indian subcontinent countries, there may be a risk of exposure to malaria. If there is any risk, all protective measures should be used. The geographic distribution and specific drug sensitivities of malaria parasites can change rapidly: the most recent information about drug patterns must be sought before prescribing chemoprophylaxis (www.cdc.gov/travel).

i. For suppression of malaria in nonimmune individuals temporarily residing in or traveling through endemic areas where, as of late 1999, the plasmodia are chloroquine sensitive (Central America west of the Panama Canal, the island of Hispaniola-Haiti and Dominican Republic-and malarious areas of the Middle East, and mainland China): chloroquine (Aralen, 5 mg base/kg body weight, 300 mg base or 500 mg chloroquine phosphate for the average adult) once weekly, or hydroxychloroquine (plaquenil, 5 mg base/kg body weight to the adult dose of 310 mg base or 400 mg salt) is recommended. Pregnancy is not a contraindication. The drug must be continued on the same schedule for 4 weeks after leaving endemic areas. Minor side effects may occur at prophylactic doses, which may be alleviated by taking the drug with meals, or changing to hydroxychloroquine. Psoriasis may be exacerbated particularly in Africans and African Americans; chloroquine may interfere with the immune response to intradermal rabies vaccine.

ii. For suppressive malaria drug therapy for travelers who will be exposed to chloroquine resistant *P. falciparum* infection (southeast Asia, sub-Saharan Africa, rain forest areas of South America, and western Pacific Islands), mefloquine alone (5 mg/kg/week) is recommended. Suppressive drug treatment should be continued weekly, starting 1-2 weeks before travel and continued weekly during travel or residence in malarious area and for 4 weeks after the return to nonmalarious areas. Mefloquine is contraindicated only in those with a known hypersensitivity to it. It is not recommended for women in the first trimester of pregnancy unless exposure to chloroquine-resistant *P. falciparum* is unavoidable (see B1(II)c viii above). Suppressive drug treatment should not be continued for more than 12 to 20 weeks, with the same drug. For those with prolonged residence in high risk areas, the seasonality of transmission and improved protective measures against mosquito bites should be weighed against the long term risk of drug reactions.

As of late 1999, mefloquine is not recommended for individuals with underlying cardiac arrhythmias, or individuals with a recent history of epilepsy, or severe psychiatric disorders. For those who are unable to take mefloquine and for those going to malaria endemic areas of Thailand (forested rural areas principally along the borders with Cambodia and Myanmar), doxycycline alone, 100 mg once daily, is an alternative regimen. Doxycycline may cause diarrhea, candida vaginitis and photosensitivity. It should not be given to pregnant women and children less than 8 years old.

Doxycycline prophylaxis can begin 1-2 days prior to travel to malarious areas and should be continued daily during travel and for 4 weeks after leaving the malarious area. Atovaquone/proguanil (Malarone™) is an alternative to mefloquine and doxycycline for travelers who will be exposed to chloroquine resistant *P. falciparum* infection: 1 adult tablet daily for adults (250 mg atovaquone/100 mg proguanil). For children 11-20 kg: 1 pediatric tablet daily (62.5 mg atovaquone/25 mg proguanil); 21-30 kg: 2 pediatric tablets daily; 31-40 kg: 3 pediatric tablets daily; >40 kg: 1 adult tablet daily. Malarone™ is contraindicated in children<11 kg, and patients of any age with severe renal insufficiency (creatinine clearance< 30ml/min). Pregnant women or women breast-feeding infants <11 kg should not use Malarone™.

Long-term travelers at risk of infection by chloroquine-resistant *P. falciparum* strains for whom mefloquine, Malarone™, or doxycycline is not recommended should take once weekly chloroquine alone. Limited data indicate that weekly chloroquine together with daily proguanil (paludrine, 200 mg) is more effective than chloroquine alone in Africa, but it cannot be expected to prevent most cases; in Asia and Oceania, proguanil adds no benefit to chloroquine alone (proguanil alone is not available in the US). Travelers in this category should carry a treatment dose of a locally effective antimalarial or Fansidar (sulfadoxine 500 mg/pyrimethamine 25 mg) unless they have a history of sulfonamide intolerance. In the event of a febrile illness when professional medical care is not readily available, they should take the complete antimalarial dosage (Fansidar-adult dose 3 tablets) and obtain medical consultation as soon as possible. It must be emphasized that such presumptive self-treatment is only a temporary measure and that prompt medical evaluation is imperative.

In areas of chloroquine resistance to both *P. vivax* and *P. falciparum*, an alternative prophylactic regimen for adults who do not have glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and women who are not pregnant and not nursing, was proposed based on clinical studies reported during the late 1990s. This regimen consists of primaquine only at 0.5 mg base/kg/day, beginning on the first day of exposure and continued for 1 week after leaving the risk area. Compliance with this regimen achieved a protective efficacy of close to 95% for *P. falciparum* and about 85%-90% for *P. vivax* in the South Pacific and South America. The most common side effect was epigastric or abdominal pain and vomiting in less than 10% of recipients. Longer term exposure, up to 50 weeks of daily administration of primaquine, showed a slight increase of methahemoglobin level to 5.8%, which declined by half within a week after ending primaquine administration.

iii. These chemosuppressive drugs do not eliminate intrahepatic parasites, so that clinical relapses of vivax or ovale malaria may occur after the drug is discontinued. Primaquine, 0.3 mg base/kg/day for 14 days (15 mg base or 26.3 mg of primaquine phosphate for the average adult) is often effective and may be given after leaving endemic areas, concurrently with or following the suppressive drug. However, it can produce hemolysis in those with G-6-PD deficiency. The decision to administer primaquine is made on an individual

basis, after consideration of the potential risk of adverse reactions, and is generally indicated only for persons who have had prolonged exposure, e.g., missionaries, Peace Corps volunteers, and some military personnel. Larger daily doses (30 mg base) are generally required for most southeast Asian, southwest Pacific, and some South American strains.

Alternatively, primaquine, 0.75 mg base/kg, may be given once weekly for 8 doses (45 mg base or 79 mg primaquine phosphate for the average adult) after leaving endemic areas. Prior to primaquine administration, the patient should be tested for G-6-PD deficiency. Primaquine should not be administered during pregnancy; chloroquine should be continued weekly for the duration of the pregnancy.

2. Control of patient, contacts and the immediate environment:

a. Report to local health authority.
b. Isolation: For hospitalized patients, blood precautions. Patients should be in mosquito proof areas from dusk to dawn.
c. Concurrent disinfection: None.
d. Quarantine: None.
e. Immunization of contacts: Not applicable.
f. Investigation of contacts and source of infection: Determine history of previous infection or of possible exposure. If a history of needle sharing is obtained from the patient, investigate and treat all persons who shared the equipment. In transfusion-induced malaria, all donors must be located and their blood examined for malaria parasites and for antimalarial antibodies; parasite positive donors should receive treatment.
g. Specific treatment for all forms of malaria:
    i. The treatment of malaria due to infection with chloroquine sensitive *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale* is the oral administration of a total of 25 mg of chloroquine base/kg administered over a 3-day period: 15 mg/kg the first day (10 mg/kg initially and 5 mg/kg 6 hours later; 600 and 300 mg doses for the average adult); 5 mg/kg the second day; and 5 mg/kg the third day. *P. vivax* acquired in Oceania may be resistant to chloroquine, in which case treatment should be repeated or a single dose of mefloquine, 25 mg/kg may be given.
    ii. For emergency treatment of adults with severe or complicated infections or for people unable to retain orally administered medication, quinine dihydrochloride, 20 mg base/kg, diluted in 500 ml of normal saline, glucose or plasma, may be administered by slow IV (over 2-4 hours); repeated in 8 hours at a lower dose (10 mg/kg) if needed, and then the lower dose is given every 8 hours until it can be supplanted by oral quinine. The pediatric dosage is the same. If there is improvement within 48 hours and drug levels cannot be monitored, each dose should be reduced by 30%; hypoglycemia is a common side effect.

    In the US, parenteral quinine is not available but parenteral quinidine can be substituted and is equally effective in treatment of severe malaria. A

loading dose of 10 mg quinidine gluconate base/kg body weight is administered by slow IV infusion over 1-2 hours, followed by a constant IV infusion of 0.02 mg base/kg/minute, preferably controlled by a constant-infusion pump, monitoring of cardiac function, and fluid balance through a central venous catheter; the quinidine infusion should be temporarily slowed or stopped for a QT interval greater than 0.6 seconds, an increase in the QRS complex by more than 50%, or hypotension unresponsive to fluid challenges. The infusion may continue for a maximum of 72 hours. All parenteral drugs should be discontinued as soon as oral drug administration can be initiated.

In extremely severe falciparum infections, particularly those with altered mental status or with a parasitemia approaching or exceeding 10%, exchange transfusion should be considered. When infections, especially severe cases, were acquired in areas where quinine resistance occurs (as of late 1999 in Thai border areas), use artemether IM (3.2 mg/kg the first day, followed by 1.6 mg/kg/day); or artesunate IV or IM (2 mg/kg on the first day, followed by 1 mg/kg/day). In hyperparasitemic cases, artesunate 1 mg/kg may be given 4-6 hours after the first dose: to limit potential neurotoxicity, it should be given for no more than 5-7 days or until the patient can take an effective antimalarial drug, such as mefloquine, 25 mg/kg, by mouth. These drugs, which are not available in the US, are used only in combination with other antimalarials.

iii. For *P. falciparum* infections acquired in areas where chloroquine-resistant strains are present, administer quinine, 30 mg/kg/day divided into 3 doses, for 3-7 days. (For severe infections, administer IV quinine as described above.) Along with quinine, administer doxycycline (2 mg/kg twice a day, maximal 100 mg/dose) or tetracycline (20 mg/kg dose, maximal 250 mg/day) given in 4 doses daily, for 7 days. Quinine may be discontinued after 3 days, except for infections acquired in Thailand and the Amazon Basin, in which case the quinine should be continued for all 7 days. Mefloquine (15-25 mg/kg) is effective for treatment of chloroquine resistant *P. falciparum* from most parts of the world, but is poorly effective on its own for *P. falciparum* in Thailand and neighboring countries. Failures have also been reported from Brazil. Every effort should be made to determine the therapeutic course producing the best results in the area where the disease was contracted, since drug resistance patterns may vary in time and locale.

iv. For *P. vivax* infections acquired in Papua New Guinea or Irian Jaya, Indonesia, mefloquine should be used for treatment (15 mg/kg in a single dose). Halofantrine is a possible alternative drug; consult package insert.

v. For prevention of relapses in mosquito acquired *P. vivax* and *P. ovale* infections, administer primaquine, as described in B1(II)e iii, above, on completion of the treatment of an acute attack. It is desirable to test all patients (especially Africans, African Americans, Asians and Mediterraneans) for G-6-PD deficiency to prevent drug induced hemolysis. Many, particularly Africans and African Americans, are able to tolerate the hemolysis, but consideration may have to be given to immediate discontinuance of primaquine: However, the induced problem must be balanced against the

possible recurrence of malaria. Primaquine is not required in nonmosquito transmitted disease (e.g., transfusion), since no liver phase occurs.

3. Epidemic measures

Determine the nature and extent of the epidemic situation. Intensify case detection as well as control measures directed against adult and larval stages of the important vectors: eliminate breeding places; treat acute cases; use personal protection and suppressive drugs. Mass treatment may be considered.

4. International measures

a. Important international measures include the following:
    i. Disinsectization of aircraft before boarding passengers or in transit by using a residual spray application of a type of insecticide to which the vectors are susceptible;
    ii. Disinsectization of aircraft, ships and other vehicles on arrival if the health authority at the place of arrival has reason to suspect importation of malaria vectors;
    iii. Enforcing and maintaining rigid antimosquito sanitation within the mosquito flight range of all ports and airports.
b. In special circumstances, administer antimalarial drugs to potentially infected migrants, refugees, seasonal workers and persons taking part in periodic mass movement into an area or country where malaria has been eliminated. Primaquine, 30-45 mg base (0.5-0.75 mg/kg), given as a single dose, renders the gametocytes of falciparum malaria noninfectious.
c. Malaria is a Disease under Surveillance by WHO, as its control is considered an essential element of the world strategy for primary health care. National health administrations are expected to notify WHO twice a year of the following:
    i. those areas originally malarious with no present risk of infection;
    ii. those malaria cases imported into areas free of disease but with continuing potential for risk of transmission;
    iii. those areas with chloroquine resistant strains of parasites; and
    iv. those international ports and airports free of malaria.
d. WHO Collaborating Centres.